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Late-Life Anemia Is Associated with Increased Risk of Recurrent Falls

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OBJECTIVES: To examine whether anemia is associated with a higher incidence of recurrent falls.

DESIGN: Prospective cohort study.

SETTING: Community-dwelling sample in the Netherlands.

PARTICIPANTS: Three hundred ninety-four participants aged 65 to 88 from the Longitudinal Aging Study Amsterdam.

MEASUREMENTS: Anemia was defined according to World Health Organization criteria as a hemoglobin concentration less than 12 g/dL in women and less than 13 g/dL in men. Falls were prospectively determined using fall calendars that participants filled out weekly for 3 years. Recurrent fallers were identified as those who fell at least two times within 6 months during the 3-year follow-up.

RESULTS: Of the 394 persons, 11.9% (18 women and 29 men) had anemia. The incidence of recurrent falls was 38.3% of anemic persons versus 19.6% of nonanemic persons ($P = .004$). After adjustment for sex, age, body mass index, and diseases, anemia was significantly associated with a 1.91 times greater risk for recurrent falls (95% confidence interval = 1.09–3.36). Poor physical function (indicated by muscle strength, physical performance, and limitations) partly mediated the association between anemia and incidence of recurrent falls.

CONCLUSION: Late-life anemia is common and associated with twice the risk of recurrent falls. Muscle weakness and poor physical performance appear to partly mediate this association. *J Am Geriatr Soc* 53:2106–2111, 2005.

Key words: anemia; falls; physical function; muscle strength; longitudinal study

Falls and fall-related fractures are a major public health problem in older people. Thirty percent of people aged 65 and older fall at least once a year, and 15% fall at least twice a year.^{1–3} It has been well established that falls and fractures are among the principal causes of disability, admission to institutional care, and mortality in older people.^{4–6} Examining treatable risk factors might help to develop preventive strategies. Anemia may be such a treatable risk factor for falls and fractures.

Anemia, defined by the World Health Organization (WHO) as a hemoglobin concentration less than 12 g/dL in women and less than 13 g/dL in men,⁷ is common in old age, with a prevalence of approximately 11% in persons aged 65 and older.⁸ A majority of anemia in old age is assumed to be due to underlying disease, such as cancer, chronic renal disease, or congestive heart failure; malnutrition; or iron deficiency,^{9,10} although in about 30% of the cases, it is not possible to directly attribute anemia to these factors.^{8,11}

Recently, anemia in old age has received increasing research attention. Symptoms of anemia include low energy, fatigue, dizziness, and general weakness. In addition, late-life anemia is associated with subsequent physical decline, as illustrated by increased disability, impaired performance, and muscle weakness.^{12–14} Through these consequences, anemia could result in an increased risk for subsequent falls, although research that confirms such a potential link is limited. The only report so far that has described a link between anemia and falls used a self-reported diagnosis of anemia, an unreliable measure with high rates of underdiagnosis.¹⁵

The present study examined whether anemia, assessed using serum hemoglobin concentration, was associated with incident falls during a follow-up period of 3 years. In addition, the potential role of dizziness, orthostatic hypotension, muscle weakness, poor physical performance, and

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disability as mediators in the association between anemia and falls was examined.

METHODS

Study Sample

Data for this study are from the Longitudinal Aging Study Amsterdam, an ongoing cohort study on predictors and consequences of changes in health in the aging population in the Netherlands. The sampling design and data collection methods have been described in detail previously.^{16,17} Briefly, a random sample of 3,107 older men and women (aged 55–85) stratified by age, sex, and urbanization, was enrolled in 1992 or 1993. Recruitment took place in three different regions in the Netherlands. From 1995 to 1996, 2,303 (87.2%) of the 2,639 eligible respondents completed a first follow-up interview. Loss of follow-up between the first and second cycle was mainly attributable to the death of the participants (417/3,107). Only persons aged 65 and older at the time of the first follow-up interview were invited for a medical interview that included blood collection and subsequent registration of falls. Of the 1,720 eligible respondents, 1,509 (87.7%) took part in the medical interview. Because of logistical and financial reasons, hemoglobin levels were determined in only one of the three data collection regions (Zwolle, $n = 458$). Exclusion of those without blood collection ($n = 54$) or with missing hemoglobin levels ($n = 10$) resulted in a sample of 394 subjects for the present study. The 64 excluded persons were significantly older (77.8 vs 74.9, $P = .001$) than the 394 persons in the present study but did not differ in terms of sex ($P = .20$) or the main fall outcome (incident recurrent falls as defined below: 16.7% vs 21.8%, $P = .39$).

Anemia

Venous blood samples were obtained from participants during the first follow-up, before the 3-year fall surveillance, and transported to the local laboratory (Zwolle, the Netherlands) for analysis the same day. Hemoglobin levels were determined using the Sysmex E5000 (Sysmex Corporation, Kobe, Japan). Anemia was defined using the WHO criteria:⁷ hemoglobin concentration less than 12 g/dL (7.5 mmol/L) in women and less than 13 g/dL (8.1 mmol/L) in men.

Falls

For 3 years, participants were asked to record fall events every week on a “fall calendar” and to mail the calendar page to the research institute after 3 months. They were contacted by phone if the procedure of the calendar was too complicated for them, if no calendar was returned even after a reminder, or if the calendar was completed incorrectly. Proxies were contacted if participants were not able to respond. A fall was defined as “an unintentional change in position resulting in coming to rest at a lower level or on the ground.” The number of falls occurring during 3 years of follow-up was used to describe the fall outcomes. As with previous studies,^{5,17} the main outcome was the incidence of recurrent falls. Recurrent falls were considered present if a subject fell at least two times within a period of 6 months during the 3-year follow-up. Recurrent falls have been

shown in previous studies to be associated with higher rates of fractures, consequent disability, and institutionalization,^{5,6} as in the current study.¹⁸

Covariates

Potential Confounders

Baseline sociodemographics included age, sex, and years of education. Current smoking status (yes or no) and body mass index (BMI, weight in kg divided by the square of height in m) were assessed. Indicators of baseline health status included self-reported diabetes mellitus, heart disease, osteoarthritis, stroke, cancer, and lung disease. Potential chronic renal disease was indicated by serum creatinine level, assessed using a standard creatinine Jaffe method (Roche Diagnostics, GmbH, Mannheim, Germany). Poor distant vision and hearing problems were ascertained by asking whether respondents could recognize someone's face at a distance of 4 m (with glasses if needed) and whether they could follow a conversation in a group of four persons (with hearing aid if needed).

Potential Mediators

Dizziness, muscle weakness, physical performance, mobility, and disability have been associated with an increased risk of recurrent falls in the present study sample.¹⁷ Because anemia has been shown to be associated with the development of disability and poor muscle strength and physical performance over time^{12–14} and may be accompanied by symptoms of dizziness and orthostatic hypotension, these variables may mediate the link between anemia and incident recurrent falls. Dizziness was assessed by asking whether the respondent was dizzy regularly (yes or no). Orthostatic hypotension was measured after the participant had reclined in a supine position and then stood for 1 minute and was defined as a drop of 20 mmHg or more in systolic blood pressure or a drop of 10 mmHg or more in diastolic blood pressure. Grip strength was assessed using a strain-gauged dynamometer (Takei TTK 5001, Takei Scientific Instruments Do. Ltd, Tokyo, Japan). Respondents performed two maximum-force trials with each hand. The maximum value of the right and left hand were summed and used as the final score. Level of physical performance was assessed using three physical performance tests: time needed to walk 3 m back and forth, time needed to stand up and sit down five times with arms folded across the chest, and time holding a tandem stand. For the first two tests, a score of 1 to 4 points was assigned, corresponding to the quartile of time needed. For the tandem stand, 1 point was given to those who stood less than 10 seconds and 2 points were given to those who stood at least 10 seconds. Participants who were not able to perform a test received a score of 0 points. The three tests were summed to a physical performance score (range 0–10).¹⁷ Mobility and disability were assessed using a validated questionnaire on the degree of difficulty with six activities: stair climbing, walking outside for 5 minutes without resting, getting up from and sitting down in a chair, dressing oneself, cutting one's toenails, and using personal or public transportation.¹⁹ Scores on the six questions were summed to a total score ranging from 0 to 24.

Table 1. Baseline Characteristics of Study Sample According to Anemia Status

Characteristic	No Anemia (n = 347)	Anemia (n = 47)	P-value*
Age, mean \pm SD	74.3 \pm 6.2	78.6 \pm 8.0	.001
Female, %	51.9	38.3	.08
Education, years, mean \pm SD	8.8 \pm 3.2	9.3 \pm 3.8	.34
Current smoker, %	13.0	14.9	.71
Body mass index, mean \pm SD	27.0 \pm 4.2	25.5 \pm 4.0	.03
Heart disease, %	27.1	40.4	.06
Stroke, %	7.2	8.5	.75
Diabetes mellitus, %	6.9	14.9	.06
Cancer, %	11.8	6.4	.27
Lung disease, %	13.5	23.4	.07
Osteoarthritis, %	46.1	34.0	.11
Hearing problems, %	36.9	36.2	.92
Vision problems, %	16.5	21.3	.41
Number of conditions, mean \pm SD	1.7 \pm 1.2	1.9 \pm 1.3	.16
Serum creatinine, μ mol/L, mean \pm SD	90.0 \pm 20.5	96.0 \pm 32.1	.04

* Based on chi-square statistics for categorical variables and *t* test statistics for continuous variables.

Statistical Analyses

Differences in proportions and means of baseline characteristics between persons with and without anemia were assessed using chi-square and *t* test statistics, respectively. Kaplan Meier curves compared the probability of developing incident falls during follow-up for persons with and without anemia. Cox proportional hazards analyses were used to evaluate the association between anemia and time to a recurrent fall. Persons surviving with no evidence of a recurrent fall were censored after the 3 years of follow-up. Hazard ratio (HRs) and 95% confidence intervals (CIs) were adjusted for the potential confounding covariates found to be univariately associated with anemia status. Additional Cox proportional hazards analyses were conducted to examine whether adding potential mediating covariates associated with anemia status reduced the association between anemia and the incidence of recurrent falls.

RESULTS

The mean hemoglobin level \pm standard deviation was 14.1 \pm 1.2 g/dL in the 196 men, and 13.3 \pm 1.1 g/dL in the 198 women. Overall, 47 respondents (11.9%) had anemia: 14.9% of the men and 9.1% of the women. Table 1

describes the differences in baseline characteristics according to anemia status. Anemic persons were significantly older, had significantly lower BMI and higher creatinine levels, and tended to report more heart disease, diabetes mellitus, and lung disease and less osteoarthritis.

Of the 394 respondents, 336 (85.3%) completed all 12 periods of 3 months of the 3-year fall follow-up, and only 20 (5.0%) completed less than 6 periods of 3 months. Eighty-six (21.8%) of the 394 respondents reported at least one fall. The median number of falls in persons with and without anemia was one, but persons with anemia more often experienced multiple falls (Table 2). For instance, 26.1% of the persons with anemia had five or more falls during the 3 years of follow-up, compared with 8.2% of those without anemia (*P* = .002). Recurrent falls, indicating at least two falls within a period of 6 months, occurred in 38.3% of the persons with anemia, versus 19.6% of those without anemia (*P* = .004). The incident recurrent fall rate per 1,000 person-years of follow-up was 78.3 for non-anemic and 176.3 for anemic persons (*P* = .002).

The probability of developing incident recurrent falls during 3 years of follow-up was significantly higher in persons with anemia than in those without anemia (Table 3). Cox proportional hazard analyses indicate that the risk for recurrent falls was 2.37 times higher when anemia was

Table 2. Description of Subsequent Falls According to Anemia Status

Falls	No Anemia (n = 347)	Anemia (n = 47)	P-value†
Median number of incident falls (25 th to 75 th percentile)	1.0 (0.0–2.0)	1.0 (0.0–5.0)	.08
Number of incident falls, %			
0	46.6	43.5	.002
1–2	36.1	23.9	
3–4	9.1	6.5	
≥ 5	8.2	26.1	
Incidence of recurrent falls, %*	19.6	38.3	.004
Incident recurrent fall rate/1,000 person-years*	78.3	176.3	.002

* Recurrent falls is present if a subject fell at least two times within 6 months.

† Based on chi-square statistics for categorical variables, Mann-Whitney statistics for number of incident falls, and log-rank test for incidence rates.

Table 3. Adjusted Risk for Recurrent Falls According to Anemia Status

Risk	Hazard Ratio	95% Confidence Interval	P-value
Unadjusted risk	2.37	1.40–4.01	.001
Sex- and age-adjusted risk	1.92	1.11–3.32	.02
Risk adjusted for potential confounders*	1.91	1.09–3.36	.02

* Age, sex, body mass index, heart disease, diabetes mellitus, lung disease, joint disease, and serum creatinine level.

present. Adjustment for sex and age decreased the HR for recurrent falls to 1.91. Further adjustment for other potential confounders that were found to be associated with anemia status (BMI, heart disease, diabetes mellitus, lung disease, osteoarthritis, serum creatinine) did not change the risk much. Figure 1 shows that the adjusted cumulative probability of experiencing recurrent falls was significantly higher for anemic than nonanemic persons ($P = .02$).

Whether dizziness, orthostatic hypotension, poor muscle strength, physical performance, and disability mediate the link between anemia and incident recurrent falls was explored. Mediation can only occur when there exists an association between potential mediators and anemia; Table 4 reports the associations between potential mediators and anemia status. Persons with anemia had significantly lower muscle strength and physical performance ($P = .006$ and $P < .001$, respectively) and reported more disability ($P = .002$) but did not report more dizziness or orthostatic hypotension than those without anemia. When muscle strength, physical performance, and disability were added to the Cox proportional hazards model already containing confounding variables, the relative risk (RR) for recurrent falls associated with anemia further reduced from 1.91 to 1.54 (95% CI = 0.86–2.76, $P = .14$, reducing RR 19.3%). To explore which mediating variables were most important,

a survival analysis was conducted using a forward selection procedure. In this analysis, only physical performance was included, which reduced the relative fall risk of anemia to 1.65 (95% CI = 0.94–2.92, $P = .08$, reducing RR with 13.6%). Overall, these analyses indicate that poor physical function explains part of the increased risk for recurrent falls in persons with anemia.

DISCUSSION

In this study, persons with anemia defined according to the WHO criteria experienced significantly more falls during 3 years of follow-up than persons without anemia. Anemia was associated with twice the incidence of recurrent falls, an important clinical outcome, because recurrent falls have been linked with fall-related fractures, institutionalization, and consequent disability.^{5,6} This association remained significant after adjustment for age, sex, BMI, and various comorbid conditions (adjusted relative fall risk = 1.92). Poor physical performance, muscle weakness, and disability were present significantly more often in anemic persons than in nonanemic persons and partly mediated the increased incidence of recurrent falls.

This study confirms that anemia is common in older persons. Twelve percent of the persons in the older sample fulfilled the WHO criteria for anemia. This percentage is consistent with reported prevalences of 11% in persons aged 65 and older⁸ and 13% in persons aged 70 and older.²⁰ Although the prevalence of anemia in older people is high, it should not be perceived as an inevitable consequence of aging. An underlying cause—a chronic condition or a nutritional deficiency—is found in approximately 70% of patients.^{8,11} About one third of cases of anemia in older people in the United States have no discernible cause, which has been termed unexplained anemia.⁸ To the authors' knowledge, this study is the first one that shows that anemia, as assessed using hemoglobin level, is associated with a higher incidence of falls, especially multiple falls. The only other study that reported a possible link between anemia and falls was based on self-report information on anemia.¹⁵

It was attempted to explain the link between anemia and falls by exploring several potential pathways in the analyses. Orthostatic hypotension and symptoms of chronic dizziness were not more present in anemic persons and therefore could not help explain the link between anemia and subsequent recurrent falls, although after adjusting for physical performance, muscle strength, and disability, the RR of falls decreased from 1.91 to 1.54, suggesting that these variables partially link anemia to falls. In this study, anemic persons appeared to be significantly weaker in terms of muscle strength and had poorer objectively measured physical performance than nonanemic persons. This finding coincides with those of earlier longitudinal studies that have

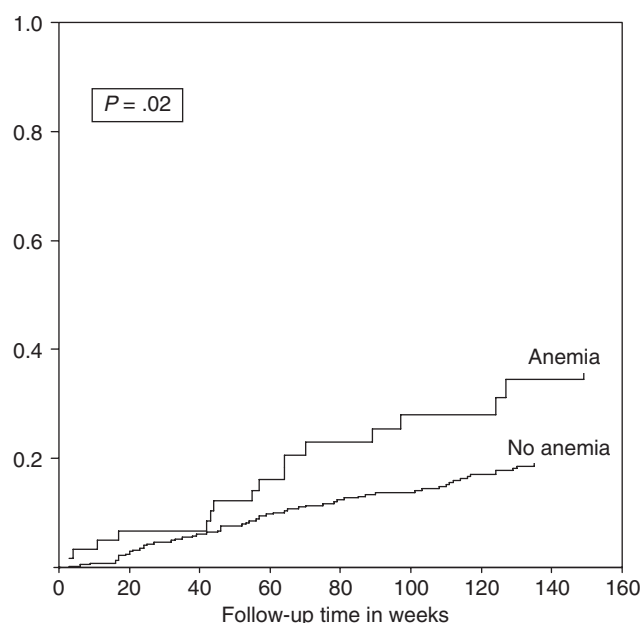


Figure 1. Adjusted hazard curve for cumulative probability to develop recurrent falls during 3 years of follow-up by anemia status. Adjusted for sex, age, body mass index, heart disease, diabetes mellitus, lung disease, joint disease, and serum creatinine level.

Table 4. Distribution of Potential Mediators According to Anemia Status

Mediator	No Anemia (n = 347)	Anemia (n = 47)	P-value*
Dizziness, %	19.0	21.3	.71
Orthostatic hypotension, %	18.7	21.7	.62
Muscle strength, kg, mean \pm SD	29.4 \pm 10.0	25.0 \pm 9.9	.006
Physical performance score, mean \pm SD	7.2 \pm 2.8	5.1 \pm 3.1	<.001
Disability score, mean \pm SD	2.9 \pm 4.5	6.0 \pm 6.1	.002

*Based on chi-square statistics for categorical variables and *t* test statistics for continuous variables.
SD = standard deviation.

shown that anemia predicts decline in physical performance independent of comorbid disease status.^{12,13}

If physical impairments and weakness partly explain why anemia is associated with more recurrent falls, how could anemia be linked with poorer physical function? Fatigue is a common symptom of anemia, which through low endurance, reduced motivation to be physically active, and subsequent deconditioning, will reduce physical function. In one study, anemia was found to be associated not only with weaker muscle strength but also with lower muscle density (more fat infiltration in the muscle) and less muscle mass.²¹ This study suggests that anemia may directly affect muscle quality. Consistent with this, some studies have demonstrated that lower levels of hemoglobin affect oxygen delivery to skeletal muscle²² and consequently affect muscular strength.²³ Moreover, anemia has been associated with higher levels of inflammatory markers,¹⁴ which may negatively affect physical performance, disability, strength, and muscle mass.^{24,25}

Some limitations of the data should be acknowledged. There was little information on nutritional status and several conditions that are known to be associated with anemia, such as liver or pancreatic disease. These unknown factors could partly account for the effect of anemia on falls. In addition, it was not possible to further characterize persons with anemia through additional tests. Finally, even though longitudinal data were used and disease and function status were adjusted for, this observational study could not prove that anemia directly affects fall risk. Anemia could still be only a manifestation of disease severity, and it could be the impairment and disability associated with disease severity that is the true link between falls and anemia. Future research should explore this further.

Nevertheless, this prospective study shows that anemia is associated with an increased risk of recurrent falls. This illustrates that it may be important to identify anemia and its cause and initiate relevant treatment to prevent the anemia from worsening. Available data have shown that successfully managing and correcting anemia in patients with chronic diseases such as congestive heart failure and chronic kidney disease improves overall prognosis.^{26,27} Future studies should explore whether treatment for anemia in other samples of older persons preserves physical function and subsequently reduces falls and fall-related injuries.

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Author Contributions: Dr. Penninx initiated the study, formulated research questions, analyzed data, and wrote the manuscript. Dr. Pluijm collected the data, assisted in data analyses and interpretation of data, and reviewed the manuscript. Dr. Lips took part in the acquisition of data, obtained funding for falls data, interpretation of data, and reviewed the manuscript. Dr. Miedema was responsible for assaying of hemoglobin and interpretation of data and reviewed the manuscript. Dr. Woodman initiated the study, took part in the interpretation of data, and reviewed the manuscript. Dr. Guralnik was involved in the interpretation of data and reviewed the manuscript. Dr. Deeg took part in the acquisition of data, obtained funding for cohort study, was involved in the interpretation of data, and reviewed the manuscript.

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